3.1 Site Core-Lab Interface Lexicon of Terms

Term	Definition
Anonymization	The process of de-identification and further removal or amiguation of information to reduce the probability of re-identification of the image despite access to other information sources
Burned-in Information	Information that is part of the actual pixel data as opposed to present in the image header.
De-identification	The process of removing real patient identifiers
De-personalization	The process of completely removing any subject-related information from an image, including clinical trial identifiers.
Image Header	That part of the file or dataset containing the image other than the pixel data itself
Individually Identifiable Information	Data that alone or in combination may be used to identify an individual.
Personal information	Data related to person identification - see EU guidances (e.g., Age)
Pseudonymization	The process of de-identification and replacement of identifiers with a pseudonym that is unique to the individual and known within the context of a trial but not linked to the individual in the external world.
Sensitive Personal Information:	Data related to personal preferences and disposition. - see EU guidances (e.g., Ethnicity).
Unique Identifiers (UIDs):	Globally unique identifier used to identifiers images, sets of images, or components within an image.

3.2 Site Core-Lab Interface – High Priority Areas

High Priority Areas:

De-identification of images and related information either by sites or by CRO on receipt from sites as an area of significant concern due to variation in privacy expectations, quality of work, conflicting or misunderstood regulation, lack of effective standards and lack of an audit trail, which would be amenable to standardization of policies, procedures, informed consent and tools, and for which there is no competitive advantage perceived.

Transfer of images from sites to sponsor and/or CROs, though an area of significant logistic cost not likely one that can be solved by standardization of tools and procedures, nor standardized in a pre-competitive manner, and which may be resolved by the evolving global trend towards cross-enterprise electronic records and off-site archiving anyway; ideally PACS vendors would implement features to facilitate clinical trials but seem to be poorly motivated by small market; table for future consideration; worth describing the ideal state (specify generic or minimal requirements); other transfer related issues of interest include reducing the burden of documentation accompanying image transfer, especially that which duplicates the image headers.

Compression specifically lossy image compression, which though theoretically undesirable and avoidable may have little impact on outcome for many types of trials, and is in practice used by many sites either during acquisition, or before archival and/or transfer and results in protocol violations; the scientific literature abounds in studies with respect to qualitative and quantitative impact for different modalities and applications and should be reviewed with respect to the possibility of defining a consensus position, or identifying areas for future research.

Digitization whilst undesirable if direct digital acquisition is available, is unavoidable in some trials due to the nature of the modality or the timing or geographic extent of the trial; accordingly quality and performance standards are needed.

Retention of images and associated information after a trial is complete and/or submitted is an area of uncertainty with respect to potentially inconsistent local, state and national regulations in global multi-center registrational trials with respect to confusion between clinical practice retention requirements (a site burden) as distinct from requirements on the sponsor and CROs for clinical trials; summarizing these requirements and/or clarifying or standardizing where gaps exist would be beneficial (may simply be a contractual matter – sponsors requirements exceed those of FDA, for example) – goal to establish good practice.

Reuse of images and associated information, either in-house (in-sponsor or in-CRO or with software contractors) or after publicly released (as is being encouraged by the government) has specific requirements on additional de-identification, and additional IRB and/or subject consent may be expected (even if not required).

Initiation and Monitoring of sites – is there a need for standard format of documentation, policies and procedures, especially for sites engaged in multiple clinical trials

Validation of software used at sites and CROs for these purposes.

3.3 Site Core-Lab Interface – Proposed Standards

1.0 Objective

To identify high priority areas of concern related to interfacing with sites with respect to image acquisition and transfer that can be addressed through pre-competitive consensus and standardization.

2.0 In Scope

- Registrational clinical trials involving the use of medical imaging (including radiology, nuclear medicine, and clinical photography)
- Human imaging only (not animals)
- In vivo imaging only
- Image-like bulk data, such as MR Spectroscopy
- Mature technologies suitable for regulatory approval
- Phantom images which are site and scanner specific for validating baseline imaging performance. These phantoms must be matched and intercalibrated in order to assure consistency among the multiple imaging sites.

3.0 Out of Scope

- Specific needs of early drug development that differ from registrational clinical trials
- In vitro (e.g. pathology imaging, whole slide, TMAs)
- Expérimental acquisition technologies (e.g. optical tomography)
- Acquisition protocols executed on the modality (being addressed by UPICT)
- Comprehensive sets of phantom images for daily quality control, and site qualification (being addressed by UPICT, NIST, ACR, SNM, ISMRM) – in table of contents only - (except for phantom and quality data transfer from sites, which is in scope)
- For the time being, image submission content and mechanics are not in scope but need to be tabled (in table of contents only).

4.0 Methodology

Consensus group of representatives from:

- Pharmaceutical and biotechnology companies
- Imaging contract research organizations
- Academic and community imaging sites
- Government (including regulators and research and standards institutes) will:
- Identify areas of concern
- Prioritize based on risk, return on investment and likelihood of consensus
- Propose standards to address areas of concern
- Seek broad consensus through public comments and meeting
- Adopt and promulgate standards (which organization, if not FDA (guidance or regulation) - DIA ? DICOM ? CDISC ? IHE ?)
- Promote adoption and acceptance of standards

5.0 High Priority Areas:

5.1. De-Identification

De-identification of images and related information received during the course of clinical trials is a major concern. Whether this process is performed by sites themselves, or by the CRO on receipt of data from sites, is of significant concern due to variation in privacy expectations, quality of work, conflicting or misunderstood regulation, lack of effective standards and lack of an audit trail. These concerns which be amenable to standardization of policies, procedures, informed consent and tools.

5.1.1 Informed Consent

In the conduct of obtaining informed consent, authorization to make use of personal information is usually obtained, as is permission to share this information with other parties involved in the trial.

There is a risk of delay or reduced enrollment if an IRB or ethics committee has privacy concerns about a particular protocol or informed consent. Regardless of actual regulations, site privacy advocates and/or risk managers may have additional requirements.

There is a benefit to use of standardized informed consent language and templates. The goal is to meet all national minimal requirements, since many multi-center trials are international, to allow for faster IRB passage, perhaps using text pre-approved by “central” IRB.

Such text should make it clear to the subject that there is always some risk of leakage of identity (no system is perfect). Some sites or nations may insist on “complete” or “absolute” de-identification and/or anonymization, but such terms are meaningless without further qualification.

See also additional requirements in the section on **Re-use.**

5.1.2. Process

Sites or CROs or both may perform de-identification and pseudonymization (true anonymization is generally not a concern for trials except during re-use).

Sites often lack consistent tools, maintain no audit trails, have no quality control procedures to ensure that de-identification is complete or pseudonymization with the correct clinical trial identifiers is performed. CROs are expect to have such tools, audit trails and procedures.

Increasingly sites are concerned about releasing data containing individually identifiable information, even if the subject has specifically authorized such release. Sponsors are increasingly concerned about possession of individually identifiable information and the risk and burden of protecting it and monitoring its use. Accordingly standards need to be set and tools need to be provided for sites to use to perform this task.

Whether or not sites perform de-identification and pseudonymization, CROs are still required to be able to perform these tasks, as well as provide oversight of the site's process. This oversight may be remotely performed (by checking the incoming data for quality and compliance with de-identification) and by monitoring (on-site evaluation of the correctness and completion).

It is undesirable (and in some cases forbidden) to collect the same information multiple times, for example to gather ethnicity on both a CRF and in the image headers. The extent to which this is a realistic or hypothetical concern or misinterpretation is unknown, but in general, the least amount of information necessary should be gathered to accompany the images.

5.1.3. What to remove

Standards need to be established for what needs to be removed and replaced during de-identification without compromising the utility of the data for the purpose of the trial. There exist standards and profiles, such as the Basic Confidentiality Profile in DICOM PS 3.15, but this needs to be specifically tailored to the needs of clinical trials. Other standards such as the IHE Teaching File and Clinical Trial Export Profile address general concerns (such as the removal of identification burned in to pixel data and the replacement of UIDs) without specifically setting standards for any particular application. The HIPAA Privacy Rule lists 18 elements that if removed are deemed to be sufficient, but removal of all of them may render the data unusable for the trial. The Privacy Rule allows for an alternative approach. The Privacy Rule also does not mandate that the data be rendered de-identified for research if the appropriate authorization has been obtained.

There may be a conflict between privacy and trial requirements. Some trials require the presence of personal information that may or may not be considered sensitive and that may or may not compromise anonymity, for example:

a) Sex and body weight are required for SUV determination in PET studies;

b) Sex and age may be required for stratification;

c) Visit (exam) dates are generally required for longitudinal comparison.

It is proposed to standardize (via the DICOM Clinical Trials Working Grouping 18) specific profiles for de-identification and pseudonymization for specific types of trials. These profiles will detail for each category of trial the specific DICOM attributes that shall be removed from the header and the specific types of burned-in identification that shall be removed. The general requirements below will need to be satisfied. Note that these requirements address both information that is explicitly identifiable, information that when linked to external data sources may compromise anonymity, and information that when linked to site data sources may compromise anonymity.

a) Explicit identifiers (name, medical record number, national identifier number, initials) shall always be completely removed;

b) Personal information that compromises anonymization, such as date of birth, shall be removed where alternative stratification information such as age at time of exam can be substituted;

c) Personal information useful for interpretation or stratification or obvious from the images, such as sex, may be retained;

d) Rounding or grouping of personal information, such as age by decade, may be used where appropriate;

e) Site and personnel information, shall be removed (e.g., the name and address of the institution or physician or operator), and if appropriate, site codes substituted;

f) Equipment identifying information of a categorical type (e.g., manufacturer and model and version) may be retained, but specific identifiers (such as device serial number) shall be removed except for those trials in which critical quality information may need to be linked to specific devices; we agree with this comment]]

g) Date information related to visits and imaging studies shall be retained if it is necessary for longitudinal comparison in the conduct of the trial – though mechanisms exist to concert dates to canonical dates and offsets, the likelihood of error by the sites is too high to allow the risk; further, there is a need to be able to match information about the same visit from disparate sources (e.g., images and clinical or lab data); one way has based algorithms exist to combine identity and date information to maintain longitudinal integrity in a anonymous manner but may be impractical to deploy routinely in a multi-center configuration;

h) Unique identifiers shall be removed and replaced with new unique identifiers, whilst retaining referential integrity amongst a set of images; the process may or may not need to be deterministic; and (perhaps based on hashing the originals)

i) All attributes whose meaning and content are uncertain shall be removed (this includes unrecognized. proprietary or private attributes in DICOM images)

The general requirements with respect to the type of information shall be equally applicable to head attributes and burned-in information. Furthermore, the risk of information stored in unexpected or inappropriate attributes shall be considered. For example, the machine operator may have included the Patient Name not just in the Patient Name attribute, but also in the Study Description; accordingly, all string fields present a risk of identity leakage. Accordingly, DICOM WG 18 will be asked to consider the feasibility of removal of all string values except where the content can be proven to be safe, e.g., by searching for and substituting specific coded values (e.g., “Chest CT” might be a legal value) and by validating the content of string numeric fields to contain only the correct characters (e.g., Study Date should be of the form “yyyymmdd” and should not contain letters).

A distinction is made between the information accompanying the image and the image of the subject itself, just as a distinction is commonly made between labels and specimens of blood or tissue. As there is a risk of re-identification from DNA comparison, there is a risk of re-identification of the images themselves (quite apart from burned in information), whether from full face photographic images or facial features potentially recognizable from 3D reconstruction of high resolution head CT or MR. Trials are underway to quantify the risk of recognition attached to such 3D reconstructions. Though processes have been proposed to de-face images without undermining their utility for some types of clinical trials, they are beyond the scope of the current discussion and will be tabled for further review when there is more information about the need and the utility.

5.1.4 Quality Control and Audit Trail

Ideally, an organization with defined and monitored processes and systems would have access to the original information as acquired from the acquisition device and would perform de-identification and pseudonymization. To the extent that these responsibilities must be divided between the sites and the CROs, the following requirements shall be satisfied:

a) any changes to data that are a consequence of passage through clinical systems at the site (such as transfer from modalities to PACS archives and workstations) shall be controlled, documented and performed using validated hardware and software only (such as approved medical devices) and shall not result in degradation (e.g., lossy compression after acquisition); note that no audit trail is expected or practical

b) any changes to data that are a consequence of clinical trial specific action, such as de-identification and pseudonymization, shall be performed using validated software, and shall result in an audit trail of the changes that shall be maintained at the site and subject to periodic monitoring; the audit trail is not required to be transferred to the CRO if the site or CRO or sponsor has privacy concerns; this process and the audit trail shall be subject to quality control and monitoring procedures to affirm the correctness of the mapping from real subject to trial specific identifiers and the completeness of de-identification (the audit trail constitutes a mapping from which original identifiers, including individually identifiable and unique identifiers may be recovered, and as such needs to be protected and archived)

c) the receiving CRO or sponsor shall perform further de-identification and pseudonymization as necessary, using validated software, and shall result in an audit trail of the changes made; leakage of identifying or sensitive information from the site shall be detected and the site queried and retrained as appropriate

d) the original images shall be archived at the site as “source data” in compliance with GCP

e) the images received by the CRO or sponsor shall be archived at the CRO or sponsor as their “source data”, or shall be fully recoverable using the audit trail information, even if the site has failed to (or was not required to) perform de-identification and pseudonymization

f) The overriding principle is to preserve the “source data” information at the appropriate location, the latter being determined by the mutually agreed upon privacy requirements.

5.1.5. IRC

The IRC should specifically document the extent of and responsibilities for de-identification and pseudonymization, quality control and the audit trail.

In particular, the IRC should address the risks to “re-identification” by those parties who will have access to the data.

5.2. Transfer

5.2.1 The transfer of images from sites to sponsors and/or CROs, between CRO and Sponsor, and to the Regulatory Agencies are out of scope for this standardization effort for the time being.

Though an area of significant logistic cost, it is not likely one that can be solved by standardization of tools and procedures, nor standardized in a pre-competitive manner

It is likely to be resolved by the evolving global trend towards cross-enterprise electronic records and off-site archiving anyway; ideally PACS vendors would implement features to facilitate clinical trials but seem to be poorly motivated by small market; such vendors have expressed reluctance to concern themselves with specific needs of clinical trials.

5.2.2 A description of the “ideal state” in which acquisition and PACS at sites might be linked to a global network of CROs and Sponsors is worthy of future consideration, particularly to the extent that requirements or information technology standards or software could be identified. Evaluation of standards such as the IHE teaching File and Clinical Trial Export Profile has been mentioned; the use of freely available open source tools such as RSNA MIRC FieldCenter could be considered, particularly with respect to what de-identification configuration is necessary to satisfy the requirements of commercial clinical trials and IRBs and ethics committees.

5.2.3 Other transfer related issues of interest for future consideration include reducing the burden of documentation accompanying image transfer, especially that which duplicates the image headers.

Evaluation of outstanding issues that make IRBs and ethics committees and hospital IT departments reluctant to provide access for such networks remains an open task.

5.3. Compression

5.3.1 Truly lossless compression, in which the original binary data is fully recoverable, is allowed under all circumstances, since the image is not in any way degraded. This is analogous to creating a compressed zip file of a document and decompressing it to recover the identical original.

5.3.2 The use of lossy (irreversible) compression raises concern that the loss (degradation) in the image, even if “visually lossless” (i.e., not obviously apparent to a human observer) may result in impaired performance.

5.3.3 The impact of lossy compression depends on the choice of compression algorithm (scheme), the parameters (compression ratio), the type of image (modality), and the interpretation or analysis task. Hence generalizations about the appropriateness of compression are dangerous. What might be appropriate for qualitative assessment may not be for quantitative assessment. Similarly contrast crude size measures versus volumetric measurements, for signal intensity measurement, for a human versus machine observer, for different sizes of lesions, or different tasks where variance due to compression may be overwhelmed by other sources of noise and variance.

5.3.4 There are no standards for compression performance. The ACR Digital Image Management guideline, for example, leaves it to the discretion of the interpreter. A review of the contemporary literature reveals no clear consensus. Many trials are subjective quality assessments rather than true observer performance studies, and are arguably meaningless. The size of a study (statistical power to distinguish real lack of difference from insufficient cases/readers) is crucial and many studies in the literature fail to address this or are likely underpowered, The relevance of the task in compression study to the question in the clinical trial must be considered. The mix of images in study (which vary in compressibility depending on noise, size (including slice thickness), dynamic range etc.) and the mix of pathological conditions may have an impact.

5.3.5 There is a strong suspicion that very modest degrees of lossy compression might not affect human observers. However there is increasing evidence that lossy compression is more likely to affect CAD (lesion detection and/or characterization).

Given this uncertainty, it is required that:

a) if a clinical trial involves a specific type of image and interpretation or measurement task that have specifically been demonstrated in a sufficiently statistically powerful not to be significantly and meaningfully influenced by a specific compression scheme and parameter choice, then such a scheme may be used, with prior documentation in the approved protocol and/or IRC

b) if the standard of care for a particular modality is to generate lossy compressed images directly at the acquisition device (e.g., for the video record of an echocardiogram), then they may be used, but without further compression

c) otherwise, if lossy compression performed at the acquisition device can be configured off, then it shall be and uncompressed or losslessly compressed images shall be used

d) no lossy compression shall be permitted subsequently, whether it be during archival at the site, retrieval or transfer to the CRO or sponsor, or in any manner prior to independent review.

Note that the DICOM header should record whether or not the image is lossy compressed, or has ever been lossy compressed (and there is a corresponding medical device approval requirement related to this), so the CRO quality control shall check for and detect evidence of lossy compression. Failure to comply with the avoidance of lossy compression is a protocol violation and such images shall result in a discrepancy report, and query of and retraining of the site.

The discrepancy report of protocol violations due to the unsanctioned use of lossy compression on a subset of subjects allows the reviewer of the results of a clinical trial to ascertain whether or not there was any impact on the outcome.

5.4. Digitization

Pure digital acquisition and transfer is preferred under all circumstances when possible to minimize loss of data from the original acquisition:

5.4.1 Quantitative analysis of signal intensity (PET SUV, MR intensity) require digital data.

5.4.2 Printed film from digital modalities should be used reluctantly if at all, and will typically be digitized prior to use.

5.4.3 Some modalities, such as projection radiography, remain analog in most parts of the world, and review on film, or film digitizations are therefore required. Standards exist already for this digitization in clinical applications. The ACR Guidline on Digital Image Management specifies that for secondary image capture:

a) Small-matrix images: Each individual image should be digitized to a matrix size as large as or larger than that of the original image on the imaging modality. The images should be digitized to a bit depth of 8 bits per pixel or greater. Film digitization or video frame grab systems conforming to the above specifications can be acceptable.

b) Large-matrix images: These images should be digitized to a matrix size corresponding to 2.5 lp/mm or greater in the original detector plane. These images should be digitized to a bit depth of 10 bits per pixel or greater.

5.4.4. Use of medical grade equipment with appropriate QC procedures is recommended.

5.4.5 Some types of film have additional specific equipment requirements (e.g., film-screen mammography film has a higher optical density than some digitizers can penetrate and higher spatial resolution requirements (e.g., <= 50 microns).

5.4.6 The IRC shall document the digitization parameters to be used for a specific study.

5.5. Retention

The retention of medical image data after a trial is complete and/or submitted for regulatory approval is an area of uncertainty with respect to potentially inconsistent country and international regulations [Code of Federal Regulations (CFR) vs. International Conference on Harmonization (ICH) – Guideline for Good Clinical Practice (GCP)].

5.5.1 Medical Image Data

The medical image data is considered an “essential document” as it can substantiate the existence, history, integrity and efficacy of the clinical trial data collected.

CFR and GCP requirements are similar as to their record retention requirements.

5.5.2 21 CFR Part 312.57

A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

5.5.3 ICH – GCP - Section 4.9

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

5.5.4 Standard Operating Procedures (SOPs)

Sponsors may also have specific Standard Operating Procedures (SOPs) requiring different (usually longer) record retention requirements.

The retention requirements of the medical image data needs to be defined for the three distinct clinical trial participants:

a) Investigational Site

b) Imaging Core Lab (ICL)

c) Sponsor

5.5.5 In addition to the record retention requirements there are other issues that need to be further defined.

a) Need to further define the specific image date to be retained by the Sites.

- Original digital data vs. film data;
- Does the site need a separate clinical trial archive vs. archiving with other daily clinical image data;
- Identifiable versus de-identified and pseuonymized image data.

b) Need to further define the specific image date to be retained by the ICL.

- Identifiable versus de-identified and pseuonymized
- Original digital data if supplied digitally
- Original film data often times needs to be returned to the sites. Only digitized copy is available.
- Original image data with full audit trail of all quantitative analysis (regions of interest and/or associated measurements) should be archived.
- Original image data with all relevant qualitative assessments should be archived.
- Image data should be retained in an acceptable standardized image file format.

c) If the Site and ICL have the medical images retained then the Sponsor does not need to retain a copy for regulatory (record retention) purposes.

d) Potential technical issues with PACS systems and archiving the data.

5.5.6 The form of archive for retention needs to be addressed, whether it be an on-line device or off-line media, and the requirements for long-term integrity of such a device.

5.5.7 Images shall be retained in a format and on media that can be read at a later point:

a) DICOM is state of the art for common modalities (MR, CT, PET)

b) If other modalities (DEXA, Visual Light images), can store in another format (if DICOM conversion gives too much overhead) but needs to be well-established standard format wherever possible

c) Exceptions may be necessary for old software and extremely new technology

d) With respect to lossy compression, if used, the images should be archived the form in which they were interpreted, not compressed subsequently.

e) Images interpreted digitally should not be stored as printed film.

5.6 Re-USE-Goals

5.6.1 Review applicable regulations on a global level (if possible) to identify requirements for data reuse

5.6.2 Solicit feedback from sampling of IRBs and ethics committees to understand their interpretation of regulations and expectations for approval and consent

5.6.3 Standardize the informed consent language in this regard without delaying approval by difficult IRBs or discouraging subject participation in clinical trial research

USA – HIPAA Privacy Rule

The topic of data reuse is closely tied to what data is being shared and used, in particular if Protected Health Information (PHI) as defined by the HIPAA Privacy Rule is planned to be shared.

De-identified data does not contain any PHI.

PHI can only be shared after obtaining written Authorization from the individual (in this case, the research subject). De-identified data can be shared without obtaining Authorization. De-identified data is defined as:

a) A data set that does not include any of the 18 elements of PHI (i.e., 'direct identifiers')

b) Have a qualified statistician determine, using generally accepted statistical and scientific principles and methods, that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by the anticipated recipient to identify the subject of the information.

The HIPAA Privacy Rule also defines a 'limited data set' that excludes most of the PHI but allows some to remain. The following table defines PHI and what PHI is permitted in a limited data set. These definitions apply to information about the individual and to information about the individual's relatives, employers, or household members.

	Description	Allowed in Limited Data Set
1	Names	
2	All geographic subdivisions smaller than a state, except for the initial three digits of the zip code if the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people	Data on town or city, state, and ZIP Code are OK
3	All elements of dates except year and all ages over 89	Full Dates OK
4	Telephone numbers	
5	Fax numbers	
6	Email addresses	
7	Social security numbers	
8	Medical record numbers	
9	Health plan beneficiary numbers	
10	Account numbers	
11	Certificate or license numbers	
12	Vehicle identifiers and license plate numbers	
13	Device identifiers and serial numbers	
14	URLs	
15	IP addresses	
16	Biometric identifiers including fingerprints and voiceprints	
17	Full-face photographs and any comparable images	
18	Any other unique, identifying characteristic or code, except as permitted for re-identification in the Privacy Rule.	OK

Of note, under the Privacy Rule, neither blood nor tissue, in and of itself, is considered individually identifiable health information; therefore, research involving only the collection of blood or tissue would not be subject to the Privacy Rule's requirements.

Limited data sets can be shared by a Covered Entity with Authorization provided a data use agreement is in place with the receiving party. A Data Use Agreement is an agreement into which the Covered Entity enters with the intended

recipient of a limited data set that establishes the ways in which the information in the limited data set may be used and how it will be protected.

IRB Approval - The Privacy Rule does not require IRB review or approval of Authorization language for research or disclosure of PHI.

ICF and Authorization - The Informed Consent Form and Authorization serve different purposes. Under the Privacy Rule, a patient's Authorization is for the use and disclosure of PHI, which can include use or disclosure for research purposes. In contrast, an individual's informed consent, as required by the HHS or FDA Protection of Human Subjects Regulations, is a consent to participate in the research study as a whole, not simply a consent for the research use or disclosure of PHI. Nevertheless, it is permitted to combine Authorization for release of PHI with the ICF of the clinical trial.

Authorization End Date -Authorization documents can indicate and end data for research with subject data or leave the end date open.

EU – Privacy Directive

TBD.

Japan

TBD.

5.6.5 Proposed Standardized Informed Consent

To initiate a discussion on standardizing the necessary language to allow for re-use, the following examples are presented for review, paraphrased from real-world examples of commercial and academic device and drug trials.

Some questions related to the examples are:

a) Is there a need to allow the subject to participate in the study but “opt out” of re-use – should these be separate documents?

b) Is there a need to emphasize that while confidentiality will be protected a guarantee can not be made that personal confidential information will not be shared?

c) Is there a need to explicitly specify the individuals and organizations that will be allowed access for re-use, or the general category of such individuals and organizations, or public accessibility for re-use ?

d) Is there a need to provide for revocation of consent for re-use, and constraint the revocation to future re-use (as opposed to uses that have already occurred) ?

e) Are there “ownership” issues ? i.e., in the US, “the site owns the record, the patient owns the information” – exactly who is consenting to what in terms of implications for re-use.

Example 1.

The sponsor plans to combine the health information obtained from subjects' study records from this and other research studies in a database. All subject information that is collected and combined will be anonymous, which means that the information cannot be linked to a specific study subject. The sponsor will use the information to help improve the device and to conduct future medical device development.

I consent to the sponsor using my personal information for future research related to this study, including anonymised database compilations.

Example 2.

The exams performed during this study may be retained for a least XX years, but without information that may identify you personally. Organizations that may inspect and/or copy your research records for quality assurance or data analysis include groups such as the XX, YY, and other organizations that have a role in this study.

Information acquired from this study may be used in the future for secondary research to advance the understanding of disease. No individual name or results that could identify you personally will be used in any reports or publications.

In respect for your privacy, all efforts will be made to keep your personal information confidential but we cannot guarantee absolute confidentially. Your personal information may be disclosed if required by law.

Example 3.

The site "http://privacyruleandresearch.nih.gov/authorization.asp#samplelang" provides sample text for the research use of health information, but does not specifically address re-use beyond the initially intended purpose, nor the re-use of de-identified data (or limited data sets).

Example 4.

If Central review for the study will be conducted please insert the following text in ICF:

When you sign this consent form you will be agreeing for the original scan to be used to assess the effect of the medication on the growth of your disease by your doctor and you will also be agreeing for a copy of your scans to be sent to XXX for independent review of your data.

Optional wording to be included in "How will my personal data be used" section:

In order to process the radiology scans, the vendor may have access to some of your personal identifying information. The vendor will maintain confidentiality by removing all the personal identifying information on your radiology scans.

For an exploratory end-point analysis (academical collaboration) the following wording was incorporated in the ICF and received IRB approval.

MRI or CT scans will be performed in this study to assess your tumor(s) size and location. The results from these scans may also be used by your physician, by the sponsor or its research partners for development of new scanning methods for possible use in future patients. Your scan results will not be given to any other parties.

5.7 Initiation and Monitoring

In order to ensure that reliable and consistent image data are acquired during the course of clinical trials, it is necessary that certain elements be put in place prior to the first patient scan at each trial site. In particular:

5.7.1 At least one representative from Radiology should be involved in site initiation activities, and a primary Radiology point of contact should be established

5.7.2 Clear communications should be established between the Radiology point of contact, the site principal investigator, the imaging CRO (if any), and the study sponsor.

5.7.3 A thorough assessment of the imaging equipment, data handling capabilities, and site personnel should be carried out to ensure that the site is capable of supporting the defined imaging protocol.

5.7.4 The Radiology point of contact should be provided with documentation detailing procedures for patient preparation, data acquisition, data handling, and transfer of image data to the imaging CRO. Training should be provided to ensure that all documentation and trial procedures have been understood, and that Radiology is willing and able to comply with the protocol and data handling procedures.

5.7.5 Where verification of quantitation or spatial resolution/uniformity is an important factor in the trial, a specific qualification step using a phantom designed to test these aspects of image acquisition should be carried out.

5.7.6 In complex protocols where the parameters differ significantly from clinical practice, site compliance to acquisition and data transfer guidelines should be verified through a test transfer prior to first patient scanning.

5.7.7 In other studies, compliance should be assessed based on the first subject scanned.

Once sites have begun collecting image data, it is important to monitor the quality of data being acquired, and to verify continued adherence to the defined imaging protocol. It is recommended that either the study sponsor or the imaging CRO:

5.7.8 Review data for quality purposes as it is collected in order to catch and correct any protocol deviations with minimal data loss.

5.7.9 Provide immediate feedback to the site Radiology point of contact regarding protocol deviations, errors in data transfer, etc.

5.7.10 Provide additional training when warranted due to changes in site personnel and repeated protocol deviations inclusive.

5.7.11 Maintain periodic communication with the site Radiology point of contact, particularly during periods of low patient accrual.

5.7.12 Recalcitrant sites (or all sites for particularly demanding protocols) may need actual on-site monitoring by sponsor, CRO or other third party, specifically directed to failure to transfer images at all or in a timely manner, correction of repeated protocol violation, re-training, monitoring of compliance with source document retention policy and use of trained and qualified staff.

5.7.13 The IRC should specify explicitly whether, when the baseline violates the acquisition parameters, subsequent time points return to the protocol-specified parameters rather than repeating the same "incorrect" exam.

5.8 Validation

- Applicability of recent FDA guidance entitled “Computerized Systems Used in Clinical Investigations” (http://www.fda.gov/cder/guidance/7359fnl.htm) to CRO software and site software and medical devices. E.g., for de-identification in sites, communicating with PACS to central lab, etc. Is this within the scope of the FDA to regulate or be concerned about.